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EXPAREL™, A BUPIVACAINE EXTENDED-RELEASE MULTIVESICULAR LIPOSOMAL FORMULATION, EXHIBITS PHARMACOKINETIC PROPERTIES CONSISTENT WITH SUSTAINED RELEASE CHARACTERISTICS

Neil Singla[1], Lakshmanasamy Somasundaram[2], Jeff Gadsden[2], William Kramer[3], Admir Hadzic[2]

[1]Lotus Clinical Research, Pasadena, CA; [2]St. Luke's Hospital, New York, NY; [3]Kramer Consulting LLC, North Potomac, MD

ABSTRACT

Objective(s): Liposomal drug-containing formulations are designed to provide slow release of drug over an extended period of time, thus extending duration while diminishing high plasma levels. In this study, we analyzed the pharmacokinetic properties of an investigational extended-release multivesicular liposomal formulation of bupivacaine (DepoFoam bupivacaine, DB, proposed proprietary name, EXPAREL™) after a single injection.

Methods: Pooled data in 446 individuals (age 18–85; 63% male) from eleven Phase 1, 2, and 3 studies were analyzed for T_{max}, $t_{1/2}$, C_{max}, and other pharmacokinetic parameters for conventional or extended-release bupivacaine. Routes of administration included wound infiltration, subcutaneous, epidural, and nerve block. Surgical models included hemorrhoidectomy, herniorraphy, bunionectomy, and total knee arthroplasty. Doses ranged from 75 to 750 mg.

Results: DepoFoam bupivacaine had an early peak concentration from 0.25–2 hours (likely due to the small amount of extraliposomal bupivacaine present in the formulation). This was followed by a slow and prolonged release of bupivacaine from DepoFoam resulting in a second peak that occurred at a median time from 12–24 hours after injection. After wound infiltration, $t_{1/2}$ lasted up to 34.1 hours for DepoFoam bupivacaine. Highest mean C_{max}, obtained after local administration of 600 mg DepoFoam bupivacaine, was 935 ng/mL (2- to 4-fold below bupivacaine's minimal toxicity thresholds).

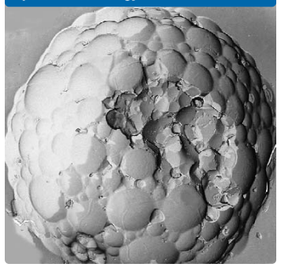
Conclusions: DepoFoam bupivacaine exhibited pharmacokinetic properties consistent with a sustained-release formulation after a single injection. Plasma concentration remained well below bupivacaine's reported toxic levels, even with DepoFoam bupivacaine doses up to 600 mg.

Summary: DepoFoam bupivacaine is a multivesicular form of bupivacaine which exhibits pharmacokinetic properties consistent with sustained release.

INTRODUCTION

- Local anesthetics/analgesics are commonly used as part of a multimodal therapy for pain management
- Bupivacaine, which has been shown to reduce postsurgical pain when used via infiltration, is the longest acting local anesthetic/analgesic, but is limited to a duration of 7 hours or less[1]
- A medical need exists for a local anesthetic/analgesic that can extend the duration of pain relief following surgery
- DepoFoam® is a proven product delivery technology that encapsulates drugs without altering their molecular structure and then releases them over a desired time period (**Figure 1**); it is used in two commercially available products in the US and ex-US
- DepoFoam bupivacaine (DB) uses multivesicular DepoFoam technology to release bupivacaine over several days, providing up to 72 hours of pain relief

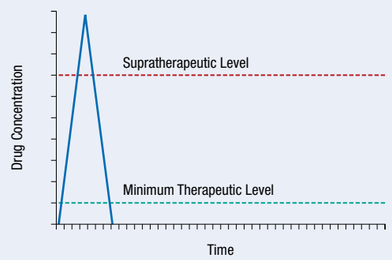
Figure 1. DepoFoam Multivesicular Liposome Technology



Conventional vs Sustained-Release Formulations

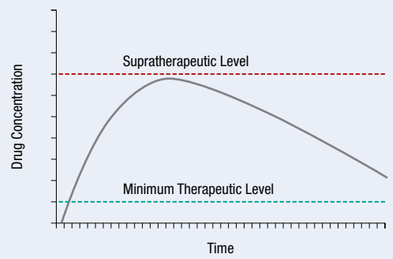
- Conventional formulations reach maximum plasma concentration (C_{max}) in a relatively short time period (T_{max}). These pharmacokinetic (PK) parameters are consistent with a rapid onset of action, a high—and often times supratherapeutic—C_{max}, and a relatively quick offset below the therapeutic threshold (**Figure 2**)

Figure 2. Release Profile of Conventional Formulations



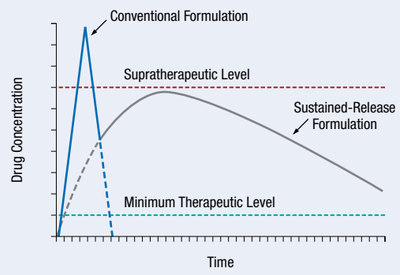
- Sustained-release formulations are characterized by a lower overall C_{max} and a longer duration of action, but the increased T_{max} can result in a longer time to onset (**Figure 3**)

Figure 3. Release Profile of Sustained-Release Formulations



- A formulation that could marry the benefits of conventional and sustained-released delivery technologies while solving the challenges associated with each would address an unmet need in the multimodal pain management landscape (**Figure 4**)

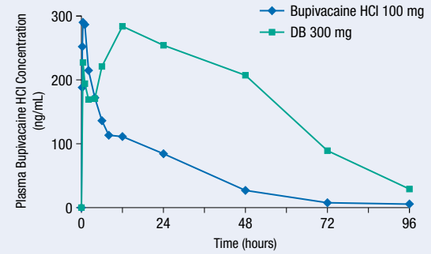
Figure 4. The Ideal Formulation Would Provide a Rapid Onset and Sustained Duration of Action



- DB is formulated to provide a longer duration of efficacy and lower plasma concentration characteristic of sustained-release formulations, while also including extraliposomal bupivacaine for rapid absorption into the systemic circulation, thereby eliminating time to onset concerns
- As demonstrated in 2009 data presented at the International Anesthesia Research Society, a single administration of DB intraoperatively resulted in a comparable time to onset (5 minutes) to bupivacaine HCl, with sustained plasma bupivacaine concentrations in subjects undergoing inguinal hernia repair (**Figure 5**)

Figure 5. DepoFoam Bupivacaine Exhibits a Rapid Onset of Action and a Sustained Release[2]

	Time to Onset	Peak	Duration
Bupivacaine HCl 100 mg	5 minutes	0–1 hour	8 hours
DB 300 mg	5 minutes	P1: 0–2 hours P2: 12–24 hours	72 hours



DB = DepoFoam bupivacaine.

PURPOSE OF ANALYSIS

- To examine the PK parameters, including C_{max}, T_{max}, and half-life ($t_{1/2}$), of traditional bupivacaine compared with DB in order to determine whether DB exhibits PK parameters consistent with sustained-release formulations, including this bimodal distribution

METHODS

- PK data from a total of 446 individuals receiving 75- to 750-mg of bupivacaine or DB across eleven Phase 1, 2, and 3 studies were analyzed
- Data were collected for multiple routes of drug administration, including wound infiltration, subcutaneous, epidural, and nerve block
- Various surgical models where DB was investigated in wound infiltration were studied, including:
  - Hemorrhoidectomy, herniorraphy, bunionectomy, and total knee arthroplasty
  - A single injection of DB was given at the conclusion of the case

RESULTS

- Independent of route of administration or surgical model studied, DB exhibited PK properties consistent with a bimodal release, as evidenced by the initial peak in plasma concentration due to the presence of extraliposomal bupivacaine, followed by the second, sustained release of the drug over a long T_{max}
  - These data indicate DB can be used in a variety of soft tissue and bony surgeries
- Consistent plasma curves were observed for all doses of DB, suggesting that dosing can safely be adapted to meet the specific needs of each surgical model
- A small amount of extraliposomal bupivacaine is present in DB to allow for rapid absorption into the systemic circulation, this is represented by the initial peak in concentration seen for each study represented in the figure (**Figure 6**)
- A slow and prolonged release of bupivacaine from DepoFoam leads up to a second peak (the C_{max}) occurring between 12 to 24 hours after administration; the $t_{1/2}$ lasts up to 34.1 hours

Figure 6. Mean Plasma Concentrations of Bupivacaine After Administration of Single Doses of DB or Bupivacaine HCl[3]

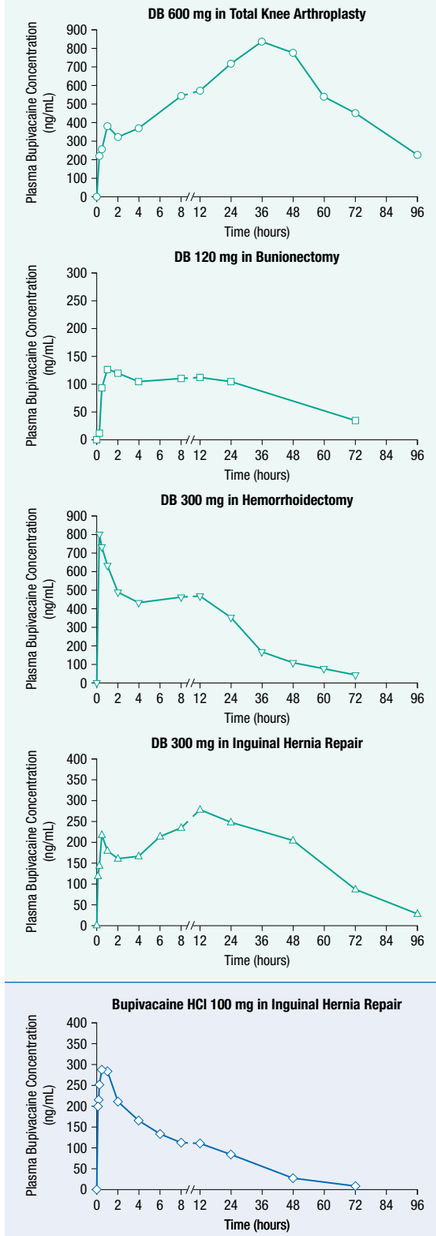


Table 1. Summary of PK Parameters for Bupivacaine After Administration of Single Doses of DepoFoam Bupivacaine or Bupivacaine HCl[3]

	DB				Bupivacaine
	120 mg <3 cm Incision	300 mg ≥3 cm Incision		600 mg Major Orthopedic/ Reconstructive	100 mg ≥3 cm Incision
	Bunionectomy (N=26)	Hemorrhoidectomy (N=25)	Inguinal Hernia Repair (N=12)	Total Knee Arthroplasty (N=16)	Inguinal Hernia Repair (N=27)
C_{max} (ng/mL)	166 (92.7)	867 (353)	365 (128)	935 (371)	336 (156)
T_{max} (h)	2	0.5	12	36	0.6
$AUC_{(0\text{-}t)}$ (h•ng/mL)	5864 (2038)	16,867 (7868)	16,028 (5455)	58,717 (24,218)	4360 (1559)
$AUC_{(inf)}$ (h•ng/mL)	7105 (2283)	18,289 (7569)	16,758 (6288)	60,174 (25,117)	4372 (1560)
$t_{1/2}$ (h)	34.1 (17.0)	23.8 (39.4)	14.6 (4.64)	16.9 (4.78)	8.47 (2.89)

DB = DepoFoam bupivacaine; PK = pharmacokinetics.
Note: Arithmetic mean (standard deviation) except T_{max} (median).

Threshold of Toxicity

- Even at a dose of 600 mg, the C_{max} of DB was 935 ng/mL, which is 2- to 4-fold below bupivacaine's minimal toxicity threshold
- Levels of ≥2000 ng/mL of bupivacaine are where central nervous system effects are usually first seen[4]
- Levels of ≥4000 ng/mL of bupivacaine are where cardiac system effects are usually first seen

DISCUSSION

- Although bupivacaine HCl is one of the most commonly used local agents for postsurgical analgesia, its 7-hour-or-less duration of action necessitates the use of additional therapeutics to manage pain
- DB builds upon the clinical experience of bupivacaine HCl and the well-established DepoFoam carrier matrix, providing a rapid onset of pain relief while extending the traditional duration of action to up to 72 hours
- The C_{max} following local administration of DB (300 mg) is comparable to that of bupivacaine HCl (100 mg)

CONCLUSIONS

- Pooled data from eleven Phase 1, 2, and 3 clinical trials of DB illustrate a PK profile consistent with bimodal and sustained-release formulations
- An elongated T_{max}, greater $t_{1/2}$, and comparable C_{max} was demonstrated across multiple surgical models and various routes of administration
- Even at doses up to 600 mg, the mean maximal plasma concentration with DB is well within the safety threshold for bupivacaine

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